UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

007670

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Tebuthiuron

HED Project No.: 9-0296
TOX Chem No.: 366AA

FROM: Ray Landolt 12/15/89
Review Section I
Toxicology Branch II - Herbicide, Fungicide, and
Antimicrobial Support
Health Effects Division (H7509C)

TO: Cathy Erumsele, PM Team 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Mike Ioannou, Section Head 12/15/89
Review Section I
Toxicology Branch II - Herbicide, Fungicide, and
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Health Effects Division (H7509C)

and

Marcia van Gemert, Branch Chief 12/18/89
Toxicology Branch II - Herbicide, Fungicide, and
Antimicrobial Support
Health Effects Division (H7509C)

Registrant : Elanco Products Company, Letter of October 13, 1988.

Second rebuttal to the general metabolism generic data requirement cited in Toxicology Chapter of the Registration Standard for Tebuthiuron (July 1987).

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Action Requested

In response to the deficiencies cited in the March 11, 1988 review by D. Ritter, of the General Metabolism Studies submitted by Elanco October 23, 1987, "New (previously not reported) data from the existing tebuthiuron metabolism studies (MRID's 00020647 and 00020804) are now being submitted" to satisify this data requirement.

Conclusion: Classification of Data - Supplementary.

Deficiencies:

1. From the Dynamac review of October 17,1989

   a. Data from female rats are not adequate.

   b. Tissue residue studies are not adequate.

2. Unhealthy animals were used in the repeated dose segment of this study.

Background Information

The following general metabolism studies, submitted by Elanco October 23, 1987 were found deficient in the March 11, 1988 review by D. Ritter for the lack of "detailed analytical data and there were no indication as to how many animals of each species were used, except for dogs where four were used."

In addition, the sex of the rabbits and dogs was not reported and the results of the excretion study were not reported individually for the rabbit or male and female mice and rats in the following two studies cited by Elanco.

1. MRID No. 00020647 - Is a copy of the paper published in the Journal of Toxicology and Environmental Health, 1976 titled, The Metabolism of a New Herbicide, Tebuthiuron N-[5-(1,1-dimethylethyl)1,3,4-thiodiazol-2-yl]-N,N-dimethylurea in Mouse, Rat, Rabbit, Dog, Duck, and Fish.

2. MRID No. 00020804 - Metabolism Studies on EL-103 in Rats, Rabbits, Dogs, Ducks and Fish, is essentially the same study as the above published study.

The general metabolism study (MRID No. 408491-01) submitted by Elanco October 13, 1988 consists of a resubmission of the two studies cited above, with the addition of the "New (previously not reported) data* from the existing tebuthiuron metabolism studies (MRID Nos. 00020647 and 00020804)".

*The date for the "previously not reported data" was not reported.

This additional data consists of,

1. a comparison of the rate and route of elimination between two male and two female rats *,
2. an additional dose level (160 mg/kg) administered to male mice and rats,
3. male rats of the 2-year chronic/oncogenicity study (No. R-603) were dosed at 10 and 160 mg/kg,
4. bile excretion following a single oral dose to three female rats**and
5. the tissue distribution in male rats dosed at 10 and 160 mg/kg were reported in this study (MRID 408491-01).

The 2-year rat chronic/oncogenicity study No. R-603 and a replicate study No. R-613, were reevaluated by D. Ritter, March 13, 1987 and appended to the Toxicology Chapter of the Registration Standard for Tebuthiuron (July, 1987). These 2-year rat chronic/oncogenicity studies were found supplementary with following deficiencies:

1. Inadequate survival (less than 25%) at 24 months.
2. Numerous instances of "unthrifty" animals.
3. Lack of a tissue inventory.

Subsequently, these studies were reevaluated by Quang Q. Bui, December 2, 1988 (copy attached) with the following conclusion:

> "Animals in this study had a high incidence of intercurrent disease and were treated with antibiotics during a serious outbreak. The incidence of rats with pneumonia approximates 70% in both control and treated groups and undoubtedly is less-than desirable based on today's standards. The question is whether the high incidence of pneumonia would adversely affect the study conclusions.
>
> From the data submitted, body weight, survival, and the tumor incidence apparently were not significantly affected by the health status of the animals".

While these studies (R-603 and R-613) were found acceptable and upgraded to Core Minimim, the use of animals with a questionable health status and low survival ratio ie, 8/40 males at low dietary level of study R-603, may have compromised the repeated dose segment of this General Metabolism Study, Table 3- Urinary Excretion of Radioactivity Following a 10 or 160 mg/kg Oral Dose of ^{14}C-Tebuthiuron to Naive and Chronically Treated Rats (Study No.R-603).

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*Fecal sample was lost for one of the two female rats dosed with ^{14}C-tebuthiuron.

**Bile sample was lost for one of the three female rats.

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EPA: 68D80056
DYNAMAC No.: 229-A
TASK No.: 2-29A
October 17, 1989

DATA EVALUATION RECORD

TEBUTHIURON

Metabolism in Rats, Mice, Rabbits, and Dogs

STUDY IDENTIFICATION: Hoffman, D.G. A supplementary report in support of general metabolism studies conducted with tebuthiuron (EL-103, Compound 75503). (Unpublished report, No. unspecified, prepared and submitted by E.I. Lilly and Company, Greenfield, IN; dated August 24, 1988.) MRID No. 408491-01.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Roman J Prieto

Date: 10-17-89

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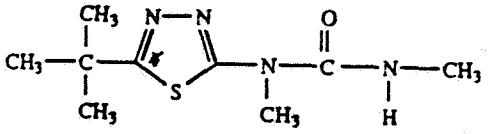
1. CHEMICAL: Tebuthiuron; 1-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-1,3-dimethylurea.

2. TEST MATERIAL: [^{14}C]Tebuthiuron labeled at C-5 of the thiodiazol ring had a specific activity 8.86 mCi/g and a radiochemical purity of 99.6 percent. The chemical structure and radiolabeled carbon (denoted by asterisk) are as follows:



3. STUDY/ACTION TYPE: Metabolism in rats, mice, rabbits and dogs.

4. STUDY IDENTIFICATION: Hoffman, D.G. A supplementary report in support of general metabolism studies conducted with tebuthiuron (EL-103, Compound 75503). (Unpublished report, No. unspecified, prepared and submitted by E.I. Lilly and Company, Greenfield, IN; dated August 24, 1988.) MRID No. 408491-01.

5. REVIEWED BY:

Nicolas P. Hajjar, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: Nicolas P Hajjar
Date: October 17, 1989

William L. McLellan, Ph.D.
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Date: October 17, 1989

6. APPROVED BY:

Roman J. Pienta, Ph.D.
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Signature: Roman J Pienta
Date: oct 17, 1989

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Ray Landolt
EPA Reviewer, Section II
Toxicology Branch I
(H-7509C)

Signature: Ray Landolt
Date: 11/9/89

Mike Ioannou, Ph.D.,
D.A.B.T.
EPA Reviewer, Section II
Toxicology Branch I (H-7509C)
EPA Section Head

Signature: Mike Ioannou
Date: 11/14/89

7. CONCLUSIONS: The metabolism of [^{14}C]tebuthiuron following administration in a single oral dose was studied in male and female rats, male mice, and female rabbits and dogs. Total recovery of radioactivity 96 hours following administration of 10 or 160 mg/kg accounted for 74 to 107 percent of the administered dose. At the low dose (10 mg/kg), most of the radioactivity was eliminated within 24 hours postdosing. Elimination in the urine accounted for 66 to 95 percent of the dose, and elimination in the feces accounted for 1.1 to 31 percent. Mice eliminated relatively less radioactivity in the urine (66 percent of the dose) and more in the feces (31 percent) than the other three species (84 to 95 percent in the urine and 1 to 13 percent in the feces). Results from a biliary excretion study in rats suggest that most of the radioactivity eliminated in feces was absorbed from the gastrointestinal tract and eliminated via the bile. Total elimination of radioactivity in male mice and rats receiving a single high dose was similar to the corresponding elimination at the low dose but occurred at somewhat slower rates. The results suggest that the high dose used does not result in saturation kinetics. Residue levels in male rats receiving the low dose were determined 4 hours postdosing, whereas residue levels in animals receiving the high dose were not performed. In a time course study, radioactivity residue levels in plasma, liver, and kidneys peaked 4 hours postdosing at the low dose and 8 hours postdosing at the high dose. Mice excrete approximately 23 percent of the urinary radioactivity as unchanged parent compound, whereas rats, rabbits, and dogs excrete 0.4 to 0.7 percent of the urinary radioactivity as unchanged parent compound indicating species differences. Fecal metabolites were not analyzed. Based on analyses of urine from all four species, a metabolic pathway was proposed for tebuthiuron.

These studies provide supplementary data on the metabolism of tebuthiuron, but do not fulfill EPA's guideline requirements. For the rat study, tissue residues were not determined, and the data from female rats were inadequate.

Items 8 through 10--see footnote 1.

1. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

1. [^{14}C]Tebuthiuron was dissolved in a minimal amount of DMSO and administered by gavage as a solution in water or as a suspension in 5 percent (w/v) acacia to mice, rats, and rabbits. Dogs received solutions of the

[1]Only items appropriate to this DER have been included.

compound in gelatin capsules. Where needed, labeled tebuthiuron was diluted with nonradioactive tebuthiuron.

2. Male and female Harlan Wistar rats (200-210 g), female Dutch-belted rabbits (2.0-2.1 kg), male ICR mice (16-20 g), and female beagle dogs (8.1-9.1 kg) were used. The source of animals was not reported. Similarly, it was not reported whether the animals were acclimated to laboratory conditions prior to dosing. Animals received 10 or 160 mg/kg of the radiolabeled test material in a single oral dose.

3. Following dosing, animals were placed in individual metabolism cages, and urine and feces were collected separately at 24-hour intervals for up to 4 days. In one experiment with rats, the animals were housed in pairs.

4. Urine samples were radioassayed directly by liquid scintillation counting (LSC). Feces were solubilized by warming in 30 percent aqueous potassium hydroxide, bleached with 30 percent hydrogen peroxide, and adjusted to pH 4.0 with hydrochloric acid prior to radioassay.

5. Urinary metabolites were separated and analyzed by thin-layer chromatography (TLC) and by gas chromatography-mass spectrometry. The metabolites and reference compounds separated by TLC were located under UV light and confirmed by autoradiography. Radiolabeled spots were scraped and radioassayed by LSC.

B. Protocol: A protocol was not presented.

12. REPORTED RESULTS:

A. Total recovery of radioactivity 96 hours following administration of [^{14}C]tebuthiuron to rats, mice, rabbits, and dogs accounted for 94 to 107 percent of the administered dose (Table 1). At the low dose, most of the radioactivity was eliminated within 24 hours postdosing. At the high dose, mice also excreted most of the administered dose within 24 hours, whereas rats eliminated equal amounts of radioactivity (34 to 37 percent) after 24 and 48 hours of dosing. Most of the radioactivity was eliminated in the urine and accounted for 66 to 95 percent of the dose. Elimination of radioactivity in the feces accounted for 1.1 to 31 percent of the dose (Table 1). Mice eliminated

TABLE 1. Elimination of Radioactivity from Animals 96 Hours Postdosing with [^{14}C]Tebuthiuron in a Single Dose at 10 or 160 mg/kg

Species	Sex	Percent of Administered Dose Recovered[a]					
		10 mg/kg			160 mg/kg		
		Urine	Feces	Total	Urine	Feces	Total
Rat	Male	94.4	1.8	96.2[c]	--[b]	--	--
	Female	92.1	2.1	94.2[c]	--	--	--
	Male	84.4	13.0	97.6	73.6	12.8	86.4
Mouse	Male	65.5	30.7	96.3[d]	82.9	23.9	106.8
Dog	Female	93.2	2.4	95.7[e]	--	--	--
Rabbit	Female	94.6	1.1	95.7[f]	--	--	--

[a]Results are the means from four animals unless otherwise stated.

[b]Not determined.

[c]Mean from two animals.

[d]Mean from seven animals.

[e]Mean from three animals.

[f]Total excretion 72 hours postdosing.

relatively less radioactivity in the urine and more in the feces than the other three species.

B. Approximately 12 percent of a 10-mg/kg dose was eliminated in the bile of two female rats 24 hours postdosing. Experimental details were not provided.

C. When tebuthiuron was administered by gavage at a dose of 10 mg/kg to groups of three male rats that had previously received the compounds in the diet for periods of 1 or 2 years, elimination of radioactivity in the urine was delayed. A higher fraction (9 to 13 percent) of the dose appeared in the 24- to 48-hour collection period when compared with animals that were not pretreated (Table 2). Similarly, elimination of radioactivity in the urine of three male rats receiving the compound in the diet for 1 year prior to dosing with 160 mg/kg [^{14}C]tebuthiuron was delayed (Table 2).

D. The distribution of radioactivity in tissues of three male rats was determined 4 hours after oral administration of a single oral dose of 10 mg/kg [^{14}C]tebuthiuron (Table 3). Four hours postdosing corresponded with peak radioactivity levels in the plasma. In addition to the high residues found in the stomach and stomach content, the highest residue levels were found in the liver, kidneys, and plasma.

E. The time-course data for radioactivity levels in the plasma, liver, and kidneys of groups of three male rats following administration of 10 or 160 mg/kg of [^{14}C]tebuthiuron are shown in Table 4. Peak concentrations occurred 4 hours after administration of the low dose and 8 hours after administration of the high dose. Thereafter, the radioactive residue levels decreased, accounting for 1.8, 5.0, and 2.4 µg/g in the plasma, liver, and kidneys, respectively, 72-hours postdosing with the high dose.

F. Following acid hydrolysis and extraction with ethyl acetate, total recovery of urinary radioactivity accounted for 86, 95, 96, and 93 percent of the administered dose in mice, rats, rabbits, and dogs, respectively. The metabolic profiles were qualitatively similar for rats, rabbits, and dogs. A total of eight metabolites were detected in the urine in addition to small amounts of unchanged parent compound (Table 5). In contrast, unchanged parent compound accounted for 23 percent of the urinary radioactivity in mice, and only seven metabolites were found. Analysis of urine from rats dosed with 10 or 160 mg/kg of the test material revealed similar metabolites, but there were

Table 2

URINARY EXCRETION OF RADIOACTIVITY FOLLOWING A SINGLE 10 OR 160 MG/KG ORAL DOSE OF ^{14}C-TEBUTHIURON TO NAIVE AND CHRONICALLY TREATED RATS[a]

Previous Treatment	Time Interval	Percent of Dose in Urine 10 mg/kg Animal Number				Percent of Dose in Urine 160 mg/kg Animal Number			
None[b]		1	2	3	Mean				
	0-24	72.9	85.9	92.5	83.8				
	24-48	c	3.6	2.2	2.9				
	48-72	1.0	0.5	0.4	0.6				
	72-96	0.4	0.3	0.2	0.3				
	TOTAL	74.3	90.3	95.2	87.6				
One-year[d]		102	103	104	Mean	329	330	331	Mean
	0-24	51.6	47.8	51.1	50.2	26.5	26.0	20.1	24.2
	24-48	12.3	17.5	8.3	12.7	27.3	31.7	26.9	28.6
	48-72	1.3	1.5	1.7	1.5	12.8	12.2	18.0	14.3
	72-96	0.3	0.3	0.5	0.4	3.7	2.6	5.2	3.8
	TOTAL	65.5	67.1	61.6	64.8	70.3	72.5	70.2	70.9
Two-year[e]		102	104	124	Mean				
	0-24	78.3	94.3	49.6	74.1				
	24-48	10.6	6.1	10.7	9.1				
	TOTAL	88.9	100.4	60.3	83.2				

[a] Previously untreated adult male rats or males from Study R-603, the 2-year chronic/oncogenicity study
[b] Adult males, 200-218 g. Study R-835
[c] Sample lost
[d] Study R-603. 10 mg/kg group had received 0.04% tebuthiuron in the diet for one year. 160 mg/kg had received 0.16% tebuthiuron in the diet for one year.
[e] Study R-603. Male animals had received 0.16% tebuthiuron in the diet for two years.

Source: CBI Table 3, CBI p. 163.

Table 3

TISSUE DISTRIBUTION OF RADIOACTIVITY IN MALE RATS
4 HOURS AFTER A SINGLE ORAL 10 MG/KG DOSE OF ^{14}C-TEBUTHIURON
STUDY R-835

	µg/g or µg/ml ^{14}C-Tebuthiuron Equivalent			
	Rat Number			
Tissue	4	5	6	Mean ± S.E.
Stomach	8.5	13.1	9.0	10.2 ± 1.5
Small Intestine	6.8	7.0	6.4	6.7 ± 0.2
Large Intestine	3.2	3.2	4.4	3.6 ± 0.4
Liver	7.5	9.5	11.7	9.6 ± 1.2
Kidney	7.9	8.8	9.5	8.8 ± 0.5
Heart	4.4	5.5	7.1	5.7 ± 0.8
Fat (Perirenal)	2.3	2.4	3.3	2.7 ± 0.3
Muscle	3.3	4.4	4.8	4.1 ± 0.4
Lung	4.5	5.0	5.9	5.1 ± 0.4
Brain	3.3	3.6	4.4	3.7 ± 0.3
Spleen	3.3	4.6	5.2	4.4 ± 0.6
Testes	3.9	4.0	4.8	4.3 ± 0.3
Stomach Contents[a]	23.5	13.5	2.9	13.3 ± 5.9
Plasma	7.0	7.9	9.4	8.1 ± 0.7

[a] Percent of Administered Dose

Source: CBI Table 8, CBI p. 168.

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Table 4

TISSUE CONCENTRATION OF RADIOACTIVITY FOLLOWING A SINGLE 10 OR 160 MG/KG ORAL DOSE OF ^{14}C-TEBUTHIURON TO MALE RATS

µg/g or µg/ml ^{14}C-Tebuthiuron Equivalents

Hours	Plasma		Liver		Kidney	
	Dose (mg/kg)					
	10	160	10	160	10	160
0.5	4.0 ± 0.7	40.9 ± 3.5	8.2 ± 1.4	70.2 ± 3.9	5.7 ± 0.7	47.4 ± 5.1
1.0	7.2 ± 0.9	53.6 ± 3.2	13.1 ± 2.1	94.2 ± 7.0	10.1 ± 1.2	66.6 ± 4.8
2.0	5.9 ± 0.6	56.9 ± 3.2	9.8 ± 0.7	86.1 ± 2.4	9.1 ± 0.6	71.1 ± 5.8
4.0	8.1 ± 0.3	62.6 ± 1.4	11.7 ± 0.5	87.7 ± 2.1	10.7 ± 0.7	70.6 ± 0.6
6.0	6.9 ± 0.2	69.9 ± 6.1	10.4 ± 0.3	100.9 ± 7.5	8.9 --[a]	80.9 ± 6.0
8.0	5.5 ± 0.3	74.0 ± 9.0	8.9 ± 0.5	107.0 ±13.3	8.7 ± 0.5	83.9 ±10.6
12.0	2.1 ± 0.7	63.3 ± 7.2	3.3 ± 1.1	96.0 ±11.0	4.9 ± 1.8	77.0 ± 6.6
24.0	0.3 ± 0.03	42.7 ± 3.3	0.7 ± 0.05	62.4 ± 5.4	0.5 ± 0.09	58.6 --[a]
36.0	-	28.5 ±12.1	-	43.9 ±17.0	-	46.4 ±18.6
48.0	-	4.2 ± 1.0	-	9.3 ± 1.5	-	8.3 ± 4.0
60.0		2.5 ± 0.2		7.0 ± 0.8	-	3.8 ± 0.9
72.0		1.8 ± 0.1		5.0 ± 0.1	-	2.4 ± 0.3

[a] Mean based on two animals

Source: CBI Table 9, CBI p. 169

Table 5

SPECIES DIFFERENCES IN THE EXCRETION OF URINARY METABOLITES FOLLOWING A SINGLE ORAL DOSE OF ^{14}C-TEBUTHIURON (10 MG/KG)

Compound excreted	% Radioactivity in urine extract[a]			
	Mouse	Rat	Rabbit	Dog
Tebuthiuron	22.6	0.7	0.4	0.6
Metabolites				
A	2.5	0.2	0.1	2.9
B	15.0	10.9	15.2	4.9
C	3.0	6.1	28.8	15.0
D	0.0	11.8	0.2	3.2
E	9.4	15.0	22.8	40.2
F	27.4	36.7	20.4	14.4
G	9.5	8.5	6.8	9.2
H	9.0	10.1	5.3	9.6

[a] The radioactivity at the Rf value of the metabolite is expressed as a percentage of the total radioactivity on the plate.

End of Report

Source: CBI Table 17, CBI p. 177.

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differences in concentrations. These metabolites were identified by gas chromatography/mass spectrometry GC/MS, and a metabolic pathway for tebuthiuron was proposed (Figure 1).

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

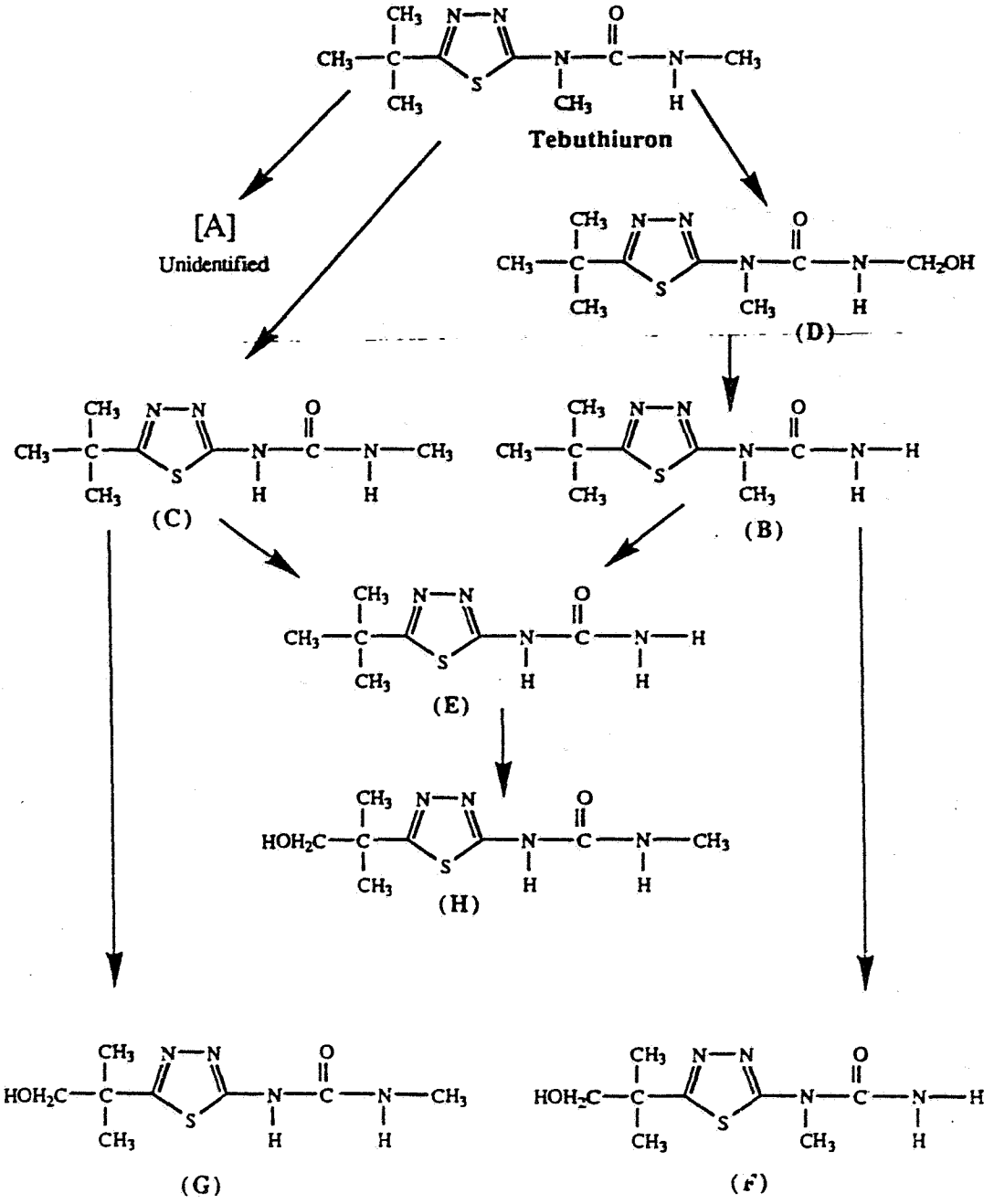
A. The above studies on the excretion of tebuthiuron differ from the current EPA guidelines, but are sufficient to describe absorption and the rate and route of excretion in male and female rats at low and high doses of the test compound after single or repeated dosing. In most cases, the studies did not use the currently required five animals of each sex per test group, but this limitation is more than adequately compensated because the experiments were repeated multiple times. The fact that there was no difference between the sexes in the first excretion study (Table 1) suggested that it was not necessary to use both sexes in all experiments. Further support for the observation that there were no differences between the sexes is the finding that the excretion pattern in female rabbits and female dogs is similar to that observed in both male and female rats.

The appearance of radioactivity in the expired air was not measured, but since recovery in urine and feces approaches 100 percent of the administered dose, this experiment would not add new information.

Tissue distribution data were obtained in only one sex (males), since earlier excretion data indicated that there was no difference in retention of tebuthiuron and its metabolites between the sexes. Except for bone, uterus, and residual carcass, all of the tissues suggested in the current EPA guidelines were examined. Distribution was determined with three animals at each time point rather than the recommended five, but there is no reason to believe that an additional two animals at each time point would materially affect the conclusions derived from these data, since wide variability between animals was not observed.

Tebuthiuron, administered orally to rats, mice, rabbits, and dogs, was readily absorbed, extensively metabolized, and rapidly excreted. After a 10-mg/kg oral dose to rats, plasma concentrations peaked at 4 hours and decreased rapidly. Elimination of radioactivity was virtually complete within 72 hours. The radioactivity, present as seven major metabolites, was excreted almost exclusively in the urine.

Figure 1.
Metabolic Pathway for Tebuthiuron



Source: CBI Figure 3, CBI p. 163.

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At a dose of 160 mg/kg, the plasma concentration was relatively constant from 1 to 12 hours after an oral dose, while excretion of radioactivity was slower than that after a 10-mg/kg dose. Importantly, the metabolites formed and excreted were identical at the two dose levels. These data indicate that absorption occurred throughout a longer period at a dose of 160 mg/kg than at 10 mg/kg, and that the metabolic processes responsible for converting tebuthiuron to excretable metabolites were saturated.

Repeated administration of tebuthiuron in the diet prior to administration of a radioactively labeled dose had no effect on the rate or route of excretion.

Tissue distribution studies demonstrated that neither tebuthiuron nor its metabolites was concentrated in any of the tissues examined. The concentrations in the tissues peaked at the same time as those in the plasma and then decreased in parallel to the plasma concentration. Not surprisingly, the liver, involved in metabolism, and the kidneys, involved in excretion, were the tissues with the highest radiocarbon concentrations. The finding that identical urinary metabolites were produced at low and high doses of tebuthiuron supports the conclusion that differences in the rate of decline of tissue residues at 10 and 160 mg/kg were the result of quantitative differences in metabolism rather than qualitative differences. The metabolism of tebuthiuron was rapid and qualitatively similar in each of the species examined. These data suggest that man would also rapidly metabolize tebuthiuron to similar metabolites.

B. A quality assurance statement was signed and dated September 27, 1988.

14. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Although extensive effort was put into the studies described, none meet EPA's guidelines. The author is apparently aware of this and attempts to explain why these studies are sufficient. It is the opinion of the reviewers that these studies provide only supplementary data on the metabolism of tebuthiuron and do not fulfill EPA's guidelines. In the first study with rats, data from females are from one pair of animals apparently housed together in metabolism cages. Data for male rats are from two pairs. Consequently, the data are means and do not provide for individual animal variations. In addition, data for male rats from the first and second experiments are considerably different. Consequently, it is not clear whether these differences are related to experimental or

biological parameters including differences between sexes.

Tissue distribution of radioactivity was determined for all tissues after only 4 hours in only three male rats receiving the low dose and does not allow for an evaluation of [^{14}C] retention and/or bioaccumulation, especially at the high dose or between sexes.

Similarly, results from studies with animals pretreated with the test material in the diet for 1 or 2 years prior to dosing with the radiolabeled test material are inadequate. Radioactivity was determined in the urine from only three males. Consequently, the number of animals used was inadequate, nc females were studied, and analysis of [^{14}C] in the feces and tissues was not performed. These studies are unacceptable.

Results from the time-course studies are unacceptable because they are not supported by appropriate tissue residue studies and cannot stand by themselves.

In addition, fecal metabolites were not identified, and consequently differences noted in mice compared with the other three species cannot be adequately explained.

Items 15 through 16--see footnote [1].